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OLL 84-4787 14 December 1984

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MEMORANDUM	FOR:	See	Dist	ribution
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VIA:	Chief, Liaison Division, OL	T ~
FROM:		
SUBTECT:	Senate Plan for Federal Ret	irement System

- 1. Attached hereto is Senator Ted Stevens'
  (R., AK) draft proposal for a Supplemental Retirement Plan for all Federal Employees hired after 31 December 1983.
  (Senator Stevens will continue to chair the Post Office and Civil Service Subcommittee of the Governmental Affairs Committee), Employees who were on the government rolls prior to 1984 and covered by the current civil service retirement system would have the option of transferring into the Stevens plan with credit for service under the old system.
- 2. This proposal is being reviewed by the Administration and selected Federal employee unions. So far, reactions have been favorable with one exception: the Administration is highly critical of the "401 K Plan" because of the cost to the government. The contributions (\$2 from government for every \$1 contributed by employee up to 4 percent of employee basic pay) would be paid out immediately, rather than only when benefits are paid out. Other concerns include: Who would appoint/approve/control the group that manages the fund; how do you deal with the potential for market manipulation, or bad investments; how do you make investment decisions? These and other issues will be discussed during the next several weeks and modifications to the draft plan will be made before it is introduced.
- 3. Senator Stevens, who plans to try again for the leadership position in 1986, wants the success of having his proposal enacted. He plans to introduce legislation in

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# DIHYDROBENZODIOXINE CARBOXAMIDE AND KETONE DERIVATIVES AS 5-HT4 RECEPTOR ANTAGONISTS

## This invention relates to compounds of formula

$$R^2$$
 $X$ 
 $N$ 
 $(CH_2)_m$ 
 $Y$ 
 $Z$ 

### wherein:

R<sup>1</sup> and R<sup>2</sup> are each independently in each occurrence hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, halogen, amino or hydroxy;

X is -NH or -CH<sub>2</sub>;

m is 2, 3, or 4;

Y is -SO<sub>2</sub>;

Z is represented by formula (A) or (B):

### wherein:

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 $R^3$ ,  $R^4$ , and  $R^5$  are each independently in each occurrence hydrogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl;

Q is O, S,  $-NR^6$ , or  $-CR^7R^8$ ;

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n is 1 or 2;

wherein:

R<sup>6</sup> is hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl, heterocyclyl, heteroaryl, -COR<sup>9</sup>, -SO<sub>2</sub>R<sup>9</sup>, -CONR<sup>10</sup>R<sup>11</sup>, -SO<sub>2</sub>NR<sup>10</sup>R<sup>11</sup>, or aryl optionally monoor di-substituted with halogen or (C<sub>1</sub>-C<sub>6</sub>)alkyl;

 $R^7$  is hydrogen or  $(C_1-C_6)$ alkyl;

 $R^8$  is hydrogen,  $(C_1-C_6)$ alkyl,  $(C_1-C_6)$ alkoxy, aryloxy,  $-(CH_2)_pCONR^{10}R^{11}$ ,  $-(CH_2)_pSO_2NR^{10}R^{11}$ ,  $-(CH_2)_pNR^7COR^9$ , or  $-(CH_2)_pNR^7SO_2R^9$ ; or

R<sup>7</sup> and R<sup>8</sup> taken together with the common ring carbon to which they are attached form a monocyclic saturated 5- or 6-membered ring optionally independently containing 0 or 1 heteroatom of nitrogen, oxygen, or sulfur;

wherein:

p is 0, 1, 2, 3 or 4;

 $R^9$  is  $(C_1-C_6)$ alkyl, heteroaryl, heterocyclyl, or aryl optionally mono- or di-substituted with halogen or  $(C_1-C_6)$ alkyl; and

 $R^{10}$  and  $R^{11}$  are each independently hydrogen or  $(C_1-C_6)$  alkyl; or individual isomers, racemic or non-racemic mixture of isomers, or pharmaceutically acceptable salts or hydrates thereof.

It has been shown that compounds of formula I are 5-HT<sub>4</sub> receptor antagonists.

5-HT (5-hydroxy-tryptamine), also referred to as serotonin, is a neuro-transmitter with mixed and complex pharmacological characteristics and was first discovered in 1948. Serotonin acts both centrally and peripherally on discrete 5-HT receptors. The 5-HT receptor family is presently delineated into seven major subclassifications, 5-HT<sub>1</sub>, 5-HT<sub>2</sub>, 5-HT<sub>3</sub>, 5-HT<sub>4</sub>, 5-HT<sub>5</sub>, 5-HT<sub>6</sub>, and 5-HT<sub>7</sub>, each of which may also be heterogeneous.

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The 5-HT<sub>4</sub> receptors are widely distributed throughout the body and have various functions. For example, the 5-HT<sub>4</sub> receptors located on postganglionic parasympathetic autonomic efferent neurons of the urinary bladder mediate facilitation of neurogenic bladder detrusor contractions (see Ford, A.P.D.W. and Kava, M.S., 5-HT4 Receptors in the Brain and Periphery; Eglen, R.M., Ed., Springer-Verlag Berlin and R.G. Landes Company Georgetown, TX, 1998, pp 171-193; Waikar, M.V. et al., Br. J. Pharmacol. 1994, 111, 213-218; Corsi, M. et al., Br. J. Pharmacol. 1991, 104, 719-725). In the central nervous system, the 5-HT<sub>4</sub> receptors are found on neurons of the superior and inferior colliculi and in the hippocampus, and are thought to be involved in areas of the central nervous system affecting anxiety, depression, cognition, dependency, schizophrenia, appetite, thermoregulation, and such. In the gastrointestinal tract, the 5-HT<sub>4</sub> receptors are found on neurons, e.g., myenteric plexus, as well as on smooth muscle and secretory cells, and appear to modulate gastrointestinal motility, evoke secretion in the alimentary tract, and stimulate cholenergic excitatory pathways involved in the peristaltic reflex (see Hegde, S.S., 5-HT4 Receptors in the Brain and Periphery; Eglen, R.M., Ed., Springer-Verlag Berlin and R.G. Landes Company Georgetown, TX, 1998, pp 150-169). In the cardiovascular system, the 5-HT<sub>4</sub> receptors mediate 5-HT induced positive inotrophy and chronotropy in atrial myocytes, e.g., bradyarrhythmia or tachyarrhythmia (see Kaumann, A. et al., Naunyn-Schmiedeberg's Arch. Pharmacol., 1991, 344, 150-159).

Thus, it is clear that 5-HT<sub>4</sub> receptor antagonists will offer distinct therapeutic advantages collectively in efficacy and rapidity of onset, particularly in urinary tract disorders related to autonomic mediation of storage and voiding reflexes. Additionally, because the 5-HT<sub>4</sub> receptors found in other organs, e.g., the heart or gastrointestinal tract, are not essential for basic physiological function, minimal side effects are anticipated with improved tolerability (see Ford, A.P.D.W. and Kava, M.S., supra).

U.S. Patent No. 5,852,014 and PCT Published Application WO 93/18036 (Gaster et al.) refer to certain condensed indole carboxamide derivatives which are disclosed as having 5-HT<sub>4</sub> receptor antagonist activity useful for treating gastrointestinal, cardiovascular, and CNS disorders.

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- U.S. Patent No. 5,763,458 (Clark et al.) and European Patent EP 0 700 383 B1 refer to certain dihydrobenzodioxine-propan-1-one derivatives which are disclosed as 5-HT<sub>4</sub> ligands.
- U.S. Patent Nos. 5,741,801 and 5,872,134, and PCT Published Application WO 94/27987 (King *et al.*) refer to certain dihydrobenzodioxine-propan-1-one derivatives which are disclosed as having 5-HT<sub>4</sub> receptor antagonist activity useful for treating gastrointestinal, cardiovascular or CNS disorders.
- U.S. Patent No. 5,708,174 and PCT Published Application WO 94/08994 (King et al.) refer to certain heterocyclic carboxylate derivatives which are disclosed as having 5-HT<sub>4</sub> receptor antagonist activity useful for treating gastrointestinal, cardiovascular, and CNS disorders.
- U.S. Patent No. 5,705,509 and PCT Published Application WO 94/17071 (Gaster et al.) refer to certain heterocyclic carboxylate derivatives which are disclosed as having 5-HT<sub>4</sub> receptor antagonist activity useful for treating gastrointestinal, cardiovascular, and CNS disorders.
- U.S. Patent No. 5,705,498 and PCT Published Application WO 94/10174 (Gaster et al.) refer to certain dihydrobenzodioxine carboxamide derivatives which are disclosed as being useful in manufacturing medicaments for 5-HT<sub>4</sub> receptor antagonists.
- U.S. Patent Nos. 5,654,320 and 5,798,367 (Catlow et al.) refer to certain indazole carboxamide derivatives which are disclosed as having 5-HT<sub>4</sub> receptor partial agonist and antagonist activity.
- U.S. Patent Nos. 5,620,992 and 5,786,372, and PCT Published Application WO 94/05654 (King et al.) refer to certain dihydrobenzodioxine carboxylate derivatives which are disclosed as having 5-HT<sub>4</sub> receptor antagonist activity.
- U.S. Patent No. 5,580,885 and PCT Published Application WO 93/05038 (King et al.) refer to certain dihydrobenzodioxine carboxamide derivatives which are disclosed as having 5-HT<sub>4</sub> receptor antagonist activity.
- U.S. Patent Nos. 5,374,637, 5,521,314, 5,536,733, 5,552,553, 5,554,772, 5,565,582, 5,576,448, 5,602,129, 5,610,157, 5,616,583, 5,616,738, and 5,739,134,

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and European Patent EP 0 389 037 B1, (Van Daele et al.) refer to certain dihydrobenzodioxine carboxamide derivatives which are disclosed as having gastrointestinal motility stimulating properties.

U.S. Patent Nos. 5,185,335 and 5,262,418 (Van Daele *et al.*) refer to certain dihydrobenzodioxine carboxamide derivatives which are disclosed as having gastrointestinal motility stimulating properties.

PCT Published Application WO 98/27058 (Bromidge *et al.*) refers to certain benzamide derivatives which are disclosed as having 5-HT<sub>6</sub> receptor activity.

PCT Published Application. WO 96/05166 (assigned to Yamanouchi) refers to certain heterocyclic-substituted alkyl-heterocycloalkylamine derivatives which are disclosed as having 5-HT<sub>4</sub> receptor agonist activity useful for treating CNS disorders and digestive tract movement.

PCT Published Application WO 94/29298 (Gaster et al.) refer to certain dihydrobenzodioxine carboxylate derivatives which are disclosed as having 5-HT<sub>4</sub> receptor antagonist activity useful for treating gastrointestinal, cardiovascular, and CNS disorders.

PCT Published Application WO 94/08995 (Gaster et al.) refers to certain heterocyclic carboxamide derivatives which are disclosed as having 5-HT<sub>4</sub> receptor antagonist activity useful for treating gastrointestinal, cardiovascular, and CNS disorders.

PCT Published Application WO 93/16072 (King et al.) refers to certain heterocyclic carboxamide derivatives which are disclosed as having 5-HT<sub>4</sub> receptor antagonist activity useful for treating gastrointestinal, cardiovascular, and CNS disorders.

PCT Published Application WO 93/03725 (King et al.) refers to certain heterocyclic carboxamide derivatives which are disclosed as having 5-HT<sub>4</sub> receptor antagonist activity.

Japanese Patent Application JP 11001472 (assigned to Dainippon Pharm) refers to certain benzamide derivatives which are disclosed as having 5-HT<sub>4</sub>

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receptor antagonist activity useful for the prevention and treatment of digestive disorders.

Japanese Patent Application JP 9241241 (assigned to Morishita Roussel) refers to certain N-(1-substituted-4-piperidyl)benzamide derivatives which are disclosed as being selective 5-HT<sub>4</sub> receptor inhibitors useful for treating chronic gastritis, CNS disorders and urological diseases.

Clark, R.D., 5-HT4 Receptors in the Brain and Periphery; Eglen, R.M., Ed., Springer-Verlag Berlin and R.G. Landes Company Georgetown, TX, 1998, pp 1-48, refers to the medicinal chemistry of certain 5-HT4 receptor ligands.

Clark, R.D. et al., Bioorganic & Medicinal Chem. Letters. 1995, 5(18), 2119-2122, refers to certain benzodioxanyl ketone derivatives having 5-HT<sub>4</sub> receptor antagonist activity.

Clark, R.D. et al., Bioorganic & Medicinal Chem. Letters. 1994, 4(20) 2477-2480, refers to certain benzoate derivatives having 5-HT<sub>4</sub> partial agonist activity.

Objects of the present invention are novel compounds of formula I, their isomers, racemic or non-racemic mixtures of isomers or pharmaceutically acceptable salts or hydrates thereof, the use in the treatment or prophylaxis of diseases, caused by 5-HT<sub>4</sub> receptors, the use of these compounds for manufacture of corresponding medicaments, processes for the manufacture of these novel compounds and medicaments, containing them. In detail, this invention relates to pharmaceutical compositions containing a therapeutically effective amount of a compound of Formula I, or individual isomers, racemic or non-racemic mixtures of isomers, or pharmaceutically acceptable salts or hydrates thereof, in admixture with one or more suitable carriers. In a preferred embodiment, the pharmaceutical compositions are suitable for administration to a subject having a disease state that is alleviated by treatment with a 5-HT<sub>4</sub> receptor antagonist.

In a preferred embodiment, this invention relates to the use in the treatment of urinary tract disorder. Such as overactive bladder, outlet obstruction, outlet insufficiency, or pelvic hypersensitivity; most preferably overactive bladder.

This invention further relates to the use in the treatment of central nervous system (CNS) disorders or gastrointestinal disorders or cardiovascular disorders.

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Unless otherwise stated, the following terms used in the specification and claims have the meanings given below:

"Alkyl" means a monovalent branched or unbranched saturated hydrocarbon radical consisting solely of carbon and hydrogen atoms, having from one to twenty carbon atoms inclusive, unless otherwise indicated. Examples of an alkyl radical include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, n-hexyl, octyl, dodecyl, tetradecyl, eicosyl, and the like. Particular values of (C<sub>1</sub>-C<sub>6</sub>)alkyl include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, n-hexyl.

"Cycloalkyl" means a monovalent saturated carbocyclic radical consisting of one or more rings, which can optionally be substituted with hydroxy, cyano, alkyl, alkoxy, thioalkyl, halogen, haloalkyl, hydroxyalkyl, nitro, alkoxycarbonyl, amino, alkylamino, dialkylamino, aminocarbonyl, carbonylamino, aminosulfonyl, sulfonylamino, and/or trifluoromethyl, unless otherwise indicated. Examples of cycloalkyl radicals include, but are not limited to, cyclopropyl, cyclobutyl, 3-ethylcyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like. Particular values of (C<sub>3</sub>-C<sub>8</sub>)cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

"Alkoxy" means a radical -OR wherein R is alkyl as defined above. Examples of an alkoxy radical include, but are not limited to, methoxy, ethoxy, isopropoxy, sec-butoxy, isobutoxy, and the like. Particular values of (C<sub>1</sub>-C<sub>6</sub>)alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentoxy, isopentoxy, and hexoxy.

"Aryl" means the monovalent monocyclic aromatic hydrocarbon radical consisting of one or more fused rings in which at least one ring is aromatic in nature, which can optionally be substituted with hydroxy, cyano, lower alkyl, lower alkoxy, thioalkyl, halogen, haloalkyl, hydroxyalkyl, nitro, alkoxycarbonyl, amino, alkylamino, dialkylamino, aminocarbonyl, carbonylamino, aminosulfonyl, sulfonylamino, and/or trifluoromethyl, unless otherwise indicated. Examples of aryl radicals include, but are not limited to, phenyl, naphthyl, biphenyl, indanyl, anthraquinolyl, and the like. A particularly preferred aryl includes phenyl.

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"Aryloxy" means a radical -OR wherein R is an aryl radical as defined above. Examples of an aryloxy radical include, but are not limited to, phenoxy and the like.

"Heteroaryl" means the monovalent aromatic carbocyclic radical having one or more rings incorporating one, two, or three heteroatoms within the ring (chosen from nitrogen, oxygen, or sulfur) which can optionally be substituted with hydroxy, cyano, lower alkyl, lower alkoxy, thioalkyl, halo, haloalkyl, hydroxyalkyl, nitro, alkoxycarbonyl, amino, alkylamino, dialkylamino, aminocarbonyl, carbonylamino, aminosulfonyl, sulfonylamino and/or trifluoromethyl, unless otherwise indicated. Examples of heteroaryl radicals include, but are not limited to, imidazolyl, oxazolyl, pyrazinyl, thiophenyl, quinolyl, benzofuryl, pyridiyl, indolyl, pyrrolyl, pyranyl, naphtyridinyl, and the like.

"Heterocyclyl" means the monovalent saturated carbocyclic radical, consisting of one or more rings, incorporating one, two, or three heteroatoms (chosen from nitrogen, oxygen or sulfur), which can optionally be substituted with hydroxy, cyano, lower alkyl, lower alkoxy, thioalkyl, halo, haloalkyl, hydroxyalkyl, nitro, alkoxycarbonyl, amino, alkylamino, dialkylamino, aminocarbonyl, carbonylamino, aminosulfonyl, sulfonylamino and/or trifluoromethyl, unless otherwise indicated. Examples of heterocyclic radicals include, but are not limited to, morpholinyl, piperazinyl, piperidinyl, pyrrolidinyl, tetrahydropyranyl, thiomorpholinyl, and the like.

"Halogen" means the radical fluoro, bromo, chloro and/or iodo.

"Protective group" has the meaning conventionally associated with it in synthetic organic chemistry, i.e., a group which selectively blocks one reactive site in a multifunctional compound such that a chemical reaction can be carried out selectively at another unprotective reactive site. Certain processes of this invention rely upon the protective groups intended to protect the nitrogen atom against undesirable reactions during synthetic procedures and includes, but is not limited to, acetyl, benzyl, benzyloxycarbonyl (carbobenzyloxy, CBZ), p-methoxybenzyloxy-carbonyl, N-tert-butoxycarbonyl (BOC), trifluoromethylcarbonyl, p-nitrobenzyloxy-carbonyl, and the like. It is preferred to use BOC or CBZ as the amino-protecting group because of the relative ease of removal, for example by